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Reduction in lesions from Lmax: a new concept for assessing efficacy of field-directed therapy for actinic keratosis. Results with imiquimod 3.75%

Background: Current parameters for assessing the efficacy of actinic keratosis (AK) treatments compare clinical lesions at the start and end of a study. However, the sun-exposed field also contains subclinical lesions which may become detectable during treatment. Lmax, the maximum lesion count during treatment, is a new concept to better assess the efficacy of field-directed AK therapies. Measuring efficacy using the reduction in lesions from Lmax includes for the first time the clearance of both subclinical and clinical lesions. **Objectives:** To evaluate the reduction of lesions from Lmax to study end and compare the results with traditional efficacy endpoints using imiquimod 3.75% (IQ3.75%) as an example of field-directed AK therapy. **Materials & Methods:** Pooled analysis of data from two 14-week, vehicle-controlled, double-blind studies of IQ3.75%. **Results:** With IQ3.75%, the median number of lesions increased from 10 at baseline to an Lmax of 22. The median absolute reduction in lesions to study end was 18 from Lmax *versus* 7 from baseline. The median percentage reduction in AK lesions to study end was 92.2% from Lmax compared with 81.8% from baseline. **Conclusions:** The reduction in lesion count from Lmax is a novel efficacy parameter that should become the new way of evaluating field-directed AK therapies since it enables their efficacy against both clinical and subclinical lesions to be accurately determined. Together, the Lmax concept and IQ3.75% represent a new approach for the management of AK across a large sun-exposed field.

Key words: actinic keratosis, efficacy assessment, field-directed therapy, imiquimod 3.75%

Our understanding of actinic keratosis (AK) has dramatically improved over recent years. It is now known that, in addition to lesions which are clinically visible, the entire area of sun-exposed skin frequently contains multiple subclinical or macroscopically invisible lesions, meaning that the entire burden of disease cannot be directly seen [1-3]. In addition, AK lesions are no longer deemed to be a cosmetic problem, but instead are considered by some experts to be *in situ* squamous cell carcinoma (SCC) which can progress into invasive SCC and which may eventually be at risk of metastasizing [1, 4-6]. Indeed, estimates indicate that over time up to 10% of AK lesions can progress into invasive SCC in immunocompetent patients and that 35–40% transform in immunocompromised patients [1].

In parallel with advances in understanding of the pathophysiology of AK, there has also been a paradigm shift in the way this disease is treated. Historically, treatment options were “lesion-directed” and based on the physical removal of clinical lesions. Conventional lesion-directed approaches include liquid nitrogen cryosurgery, curettage, shave excision and laser ablation [7]. However, given that the photodamaged skin contains both clinical and subclinical

lesions and that it is not possible to predict which lesions will develop into invasive SCC [1], European Consensus recommendations and current expert opinion advocate that subclinical and clinical lesions on large sun-exposed areas such as the full face or entire scalp must be eradicated [1, 8, 9].

Despite the progress made in understanding and treating AK, there are still several unmet medical needs. Firstly, to be a true field-directed AK therapy, the treatment must be able to effectively and safely treat large sun-exposed areas such as the full face or the entire balding scalp. However, currently available treatments have only been evaluated for use on restricted areas of these sun-exposed regions or are limited in terms of the amount that can be applied [10-16]. Secondly, there is no evidence that any of the currently available patient-applied AK treatments can eradicate subclinical lesions in addition to clinical lesions across a large sun-exposed field, e.g., the full face or entire balding scalp [10-13, 16]. Finally, current standard parameters for assessing the efficacy of AK treatments (e.g., complete or partial clearance rates and percentage change in lesions from baseline to study end) are based on the lesion-directed approach with the number of clinical lesions being compared before

and after treatment. Such assessments do not adequately reflect the latest understanding of the pathophysiology of disease in which the photodamaged skin contains both clinical and subclinical lesions and they therefore underestimate the actual benefit of a true field-directed treatment. Clearly there is a need to develop new and more appropriate efficacy parameters for field-directed AK treatments which can assess their ability to reduce not only clinically visible lesions, but also subclinical lesions across a large sun-exposed field, e.g., the full face or entire balding scalp.

Lmax, defined as the maximum lesion count during treatment, is a new concept which is being introduced to fully assess the efficacy of field-directed AK therapy. Lmax takes into account, for the first time, the clearance of lesions which are clinically visible at baseline across a large sun-exposed area e.g. the full face or entire balding scalp, and also the subclinical lesions in the same field which are invisible at baseline and which become detectable upon treatment. For individual patients, Lmax can occur at any time point during the treatment period, up to and including the last treatment application, depending on the patient's response to treatment. Efficacy is assessed by comparing Lmax with the final lesion count at study end, which is typically measured two months after the end of treatment. The theoretical advantage of this approach is that it represents a more complete measure of the efficacy of a field-directed AK therapy, in contrast to traditional efficacy parameters which compare the lesion count at study end with that at baseline and only assess the clearance of clinical lesions. The aim of the current investigation was to evaluate the reduction of lesions from Lmax to study end as a new concept for assessing the efficacy of field-directed AK therapy in comparison with traditional efficacy measures. The analysis used pooled data from two randomised, vehicle-controlled double-blind studies of imiquimod 3.75% (Zyclara[®], Meda AB, Solna, Sweden) [17]. Imiquimod 3.75% is a Toll-like receptor-7 agonist which is being developed to treat a large sun-exposed field such as the full face or entire balding scalp, with studies indicating that imiquimod not only treats clinical AK lesions but that it can also "reveal" subclinical lesions that were previously not seen in the sun-exposed field [17-19]. Imiquimod is believed to reverse the immunosuppression in the skin caused by long-term ultraviolet light exposure by stimulating an immune response which destroys AK lesions in the treated area of the skin. This immune response is mediated through increased production of cytokines such as interferon- α , interferon- γ and interleukin-12, and through involvement of immune cells [20, 21]. Imiquimod also has the potential to directly induce apoptosis in skin cancer cells [22].

Materials and methods

Study design and patients

This pooled analysis included data from two identical 14-week multicentre, vehicle-controlled double-blind phase 3 studies of imiquimod 3.75%. The details of these studies have been previously published [17]. The studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all relevant local regulations.

The study protocols and informed consents were approved by a central institutional review board or at specific institutions as required.

Patients were eligible for participation in the studies if they had 5–20 AK lesions in an area greater than 25 cm² on either their face or balding scalp. All patients provided written informed consent before participating in the studies. Patients applied up to two sachets of study cream (250 mg cream/sachet) to either the full face or balding scalp each day for two weeks. Patients were advised to apply a second sachet of treatment if needed to completely cover the treatment area; however the amount of cream that patients applied to their treatment area was not standardised (the mean consumption of sachets per patient was 1.6 for imiquimod 3.75% and 1.7 for placebo). The first treatment period was followed by two weeks without treatment and then an obligatory second two-week treatment period. Rest periods from daily treatment were allowed by the investigator as needed to manage local skin reactions or application site reactions, with resumption of treatment when the condition had adequately resolved. End of study (EOS) was eight weeks after the end of the last treatment application, i.e., at week 14.

Efficacy evaluations

Lesions were to be counted by the same investigator at each visit and were considered to be AKs if they presented clinically as rough, crusted, flesh coloured to reddish brown papules or macules, with an adherent scale in a field of sun-damaged skin. Lesions were counted at baseline and at weeks 1, 2, 4, 5, 6, 10 and 14 during the double-blind studies.

Lmax was defined as the highest or maximum lesion count during the entire treatment period (i.e., from baseline to end of treatment at week 6). Median absolute and percentage reductions in AK lesion count were calculated from Lmax to the lesion count at EOS.

Statistical analysis

The combined intent-to-treat population of all randomised patients from the two studies was used for all efficacy analyses. The original data for lesion counts at all study visits were used and missing or indeterminate lesion counts were not imputed. The Cochran-Mantel-Haenszel test stratified by study centre was used to evaluate the statistical significance of the difference in efficacy parameters between the two treatment groups.

Results

Patient population and treatment exposure

A total of 319 patients were included in the pooled analysis: 160 in the imiquimod 3.75% and 159 in the placebo group. The baseline characteristics of the two treatment groups were similar and have been published previously [17]. The mean age of the patients in the two groups was similar (imiquimod 3.75%: 64.5 years; placebo 64.3 years), most of the patients in each group were male (82.5% and 81.8%) and the median number of AK lesions at baseline in both

groups was 10. Patients in both groups used a similar mean number of treatment applications (imiquimod 3.75%: 26.2; placebo 26.8) and sachets (42.7 and 45.5) during the studies. Overall, 10.6% of patients in the imiquimod 3.75% group took a rest period from treatment.

Lesion clearance

Lmax was defined for each patient as the maximum lesion count over all time points during the entire treatment period (i.e., from baseline to end of treatment at week 6). The time point of Lmax occurrence was individual for each patient; for most patients (40%), Lmax occurred at week 2. The median values for Lmax for the imiquimod 3.75% group and placebo group were 22 and 13, respectively. This represents the median of the maximum lesion count for all patients during the treatment period and indicates that the number of AK lesions doubled during treatment with imiquimod 3.75%. The median values for Lmax for patients in the imiquimod 3.75% group who were treated for AK lesions on their face and balding scalp were similar (22 and 21, respectively).

The median AK lesion count during the course of the study is shown in *figure 1*. Lesions were counted at each particular time point. The respective medians per time point are shown in the figure. With imiquimod 3.75%, the number of AK lesions transiently increased during both periods of treatment with a greater increase during the first treatment cycle. The maximum of these medians was 18. At the end of the study, there was a median of two AK lesions in the imiquimod 3.75% group and seven in the placebo group.

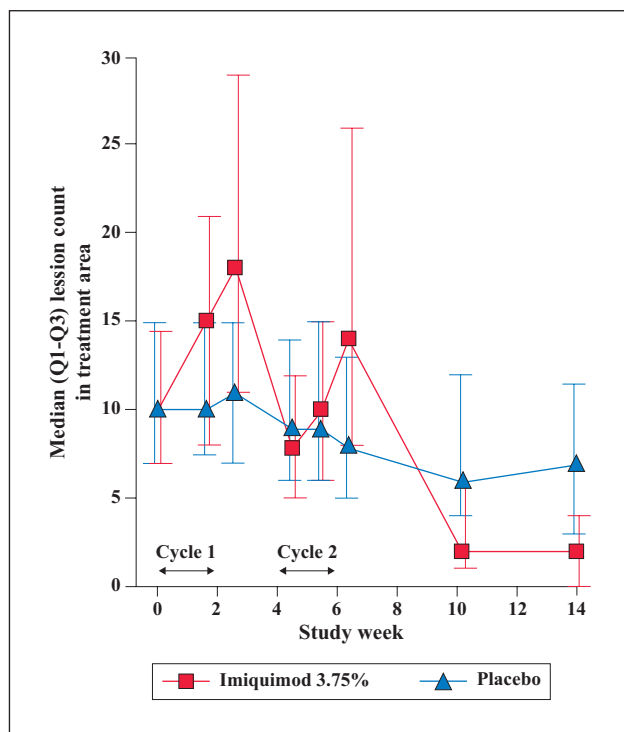


Figure 1. Median lesion count over time. Lesion count was measured at each particular time point. The respective medians per time point are displayed in the figure. The maximum of these medians was 18. Q1 = first quartile; Q3 = third quartile.

Photos from a representative patient in the imiquimod 3.75% clinical studies are shown in *figure 2*. The number of AK lesions increased during each cycle of imiquimod 3.75% treatment as subclinical lesions were unmasked with Lmax occurring at the end of the second treatment cycle in this patient. All lesions were cleared by the end of the follow-up period.

With imiquimod 3.75%, a median of 18 AK lesions were cleared from Lmax to EOS corresponding to a median percentage reduction of 92.2% of all the patients' AK lesions. This was significantly greater than the median absolute reduction in lesions and the median percentage reduction in lesions from Lmax to EOS with placebo (5 lesions and 39.3%, respectively, $P < 0.0001$ for both comparisons; *figure 3*).

Comparison of Lmax and traditional efficacy endpoints

Comparing the efficacy variables calculated from Lmax reported in this pooled analysis with the results of the traditional efficacy endpoints from the original analysis [17] (Data on file, Meda) showed that the median percentage reduction in AK lesions from Lmax to EOS was numerically greater (imiquimod 3.75%, 92.2%; placebo 39.3%) than the reduction in AK lesions from baseline to EOS (imiquimod 3.75%, 81.8%; placebo 25.0%). Similarly, the median absolute lesion reduction in AK lesions was greater from Lmax to EOS (imiquimod 3.75%, 18.0; placebo, 5.0) compared with baseline to EOS (imiquimod 3.75%, 7.0; placebo, 2.0).

Discussion

Lmax is a new concept which for the first time can more reliably assess the efficacy of a field-directed AK therapy such as imiquimod 3.75%, which can detect and treat clinical and subclinical lesions across a large sun-exposed field such as the full face or entire balding scalp. Lmax was defined for each patient as the maximum lesion count during the entire treatment period with the specific time point of Lmax occurrence depending on the individual patient's response to treatment. Unlike standard efficacy parameters, which only assess the reduction of clinical lesions, lesion clearance from Lmax takes into account the emergence and clearance of subclinical lesions which are not visible at baseline but are revealed with imiquimod 3.75% treatment. Therefore, the effect of the treatment on a large sun-exposed field such as the full face or entire scalp is evaluated leading to a more appropriate assessment of the efficacy of field-directed AK treatments.

The results of the current pooled analysis show that with imiquimod 3.75% applied as a field therapy to a large sun-exposed area such as the full face or entire balding scalp in a regimen of two treatment periods each of two weeks' duration separated by a two-week treatment free interval, the median number of lesions increased from 10 at baseline to an Lmax of 22 and decreased to 2 by EOS. The median percentage reduction in AK lesions from Lmax to EOS was 92.2%. The median baseline lesion count indicates that the patients had relatively advanced disease given

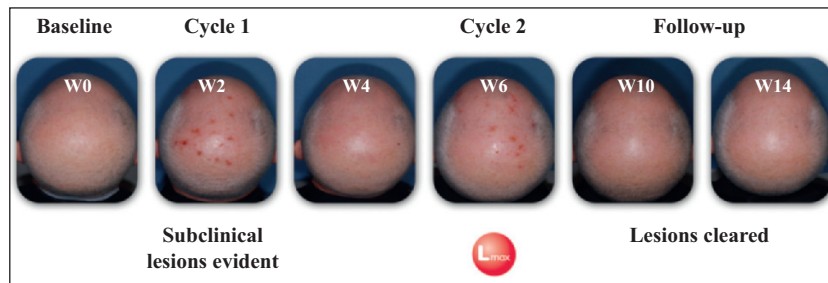


Figure 2. Patient photos illustrating Lmax, the maximum lesion count during treatment.

that studies have shown that 6–10% of patients with multiple AKs will develop malignant disease over a 10-year period [23]. The rise in lesion count in the imiquimod 3.75% group during each treatment cycle indicates that subclinical lesions became visible during treatment and therefore the overall number of detectable lesions increased. The overall reduction in lesion count by the study end suggests that imiquimod 3.75% might be able to decrease a patient's subsequent risk of progressing to invasive SCC. The reduction in lesion count from Lmax is a more complete measure of the efficacy of imiquimod 3.75% as it takes into account both the clearance of AK lesions which are clinically visible at baseline and also the subclinical lesions which become detectable during treatment. The median

absolute reduction in lesions from Lmax to EOS was 18, whereas the median absolute reduction in lesions from baseline to EOS was 7, i.e., using Lmax rather than baseline lesion count leads to a difference in absolute reduction of 11 lesions. Since standard efficacy parameters only consider lesions which are clinically visible at baseline, we can see here that the reduction in lesions from Lmax more fully represents the treatment's efficacy.

The results comparing the median percentage reduction in lesions from Lmax to EOS with those from baseline to EOS also demonstrate that the efficacy of a field-directed AK therapy is optimally assessed using the Lmax concept. With imiquimod 3.75%, the median percentage reduction in lesions was 92.2% from Lmax to EOS as compared with 81.8% from baseline to EOS. Overall efficacy is underestimated using traditional efficacy endpoints as they do not take into account the detection and clearance of subclinical lesions – a relevant pre-requisite for a true field-directed treatment for AK.

In conclusion, the reduction in lesion count from Lmax is a novel efficacy parameter which should become the new way of evaluating the efficacy of field-directed AK therapy as it takes into account the clearance of both subclinical and clinical lesions across a large treated sun-exposed field such as the full face or entire balding scalp, in contrast to traditional efficacy endpoints which only evaluate clinical lesions. As of yet, imiquimod 3.75% is the only field-directed AK treatment whose pivotal clinical data has been assessed using the Lmax concept. Results with imiquimod 3.75% show that lesion clearance from Lmax rather than from baseline enables imiquimod's actual clinical efficacy to be appropriately and accurately determined. This pooled analysis demonstrates that imiquimod 3.75% makes subclinical lesions visible and effectively treats up to 92.2% of all AK lesions on a large treated sun-exposed area such as the full face or entire balding scalp. Together, the Lmax concept and imiquimod 3.75% represent a new approach for the management of AK across a large sun-exposed field. ■

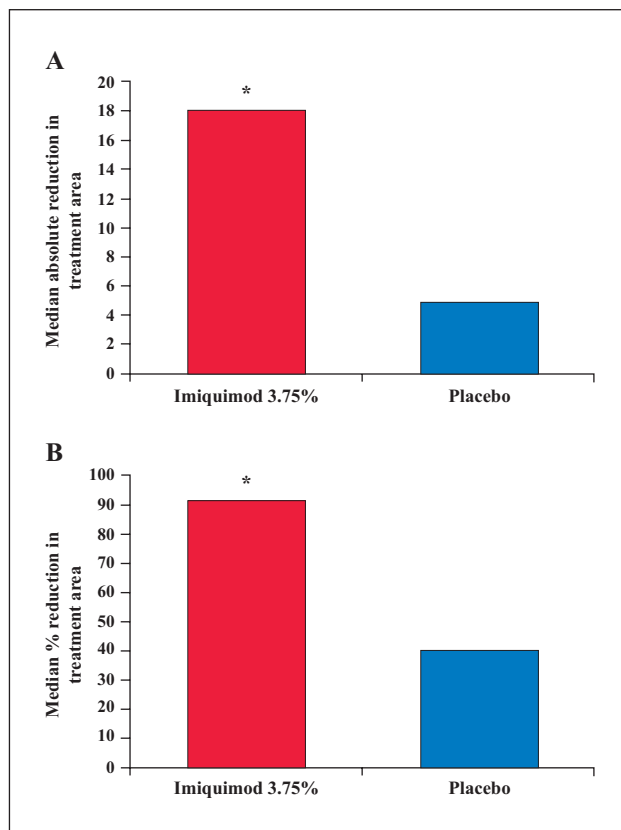


Figure 3. Reduction in lesions from Lmax to end of study. **A)** Median absolute reduction. **B)** Median percentage reduction. * $P < 0.0001$ imiquimod 3.75% versus placebo. Lmax, maximum lesion count during treatment.

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